SPLENECTOMY IN SPLENIC ANÆMIA OR PRIMARY SPLENOMEGALY.[1]

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At present little is actually known concerning the physiology and pathology of the spleen. All cases therefore, which may possibly aid in the elucidation of either or both of these subjects, should be carefully studied and placed on record. The cases which form the basis of this contribution will be given in detail first.

Case I.—Miss E. O., twenty-two years of age, born in Chicago of Swedish parents. The family history throws no light on this case. The father and mother, two sisters and one brother are living and in good health. One sister died of convulsions at the age of three years. There is no history of tuberculosis or malignant disease in the family.

When about six or seven years of age she had measles and a very mild attack of diphtheria. At eleven she had quite a severe fall from a swing. She was perfectly well thereafter until about the age of thirteen years, when she felt a sense of discomfort about the stomach, and accidentally discovered a tumor in the left side of the abdomen. She told her mother about it, but she thought it would disappear, and nothing was done.

Some six months after she discovered the tumor she had a severe sick spell lasting nearly three months. This was diagnosed by her physician as typhoid fever; but there may be some question regarding the correctness of this diagnosis, as the course of the disease, if typhoid, was very atypical.

The illness began with profuse hæmatemesis. There was pain in the

[1] Read before the Chicago Surgical Society, March 8, 1901.

abdomen with distention and fever, but at no time was there any disturbance of the bowels. During the course of the disease, which, as stated, lasted about three months, there were two other hæmorrhages from the stomach, neither of which, however, was as profuse as the first.

Some four months after getting up from this sickness, or at the age of fourteen, she was brought to the surgical clinic of Dr. Harris at the Policlinic on account of the tumor in the left side. The tumor was recognized as an enlarged spleen and a blood examination made. As the case was an out-patient, no record of the blood examination was kept.

There was no leucocytosis, however, and, after excluding leukæmia and other known causes of splenic enlargement, a diagnosis of idiopathic enlargement of the spleen was made. She was given arsenic, and improved much in general health. She was seen at intervals for about two years, then disappeared from view, the splenic enlargement remaining about the same.

At fifteen she went to work in a store. At sixteen she had another hæmorrhage from the stomach, and was off work for a time. Menstruation began at the age of seventeen, and continued in a regular and normal manner. From this time on her general health gradually failed. She became pale, reduced in flesh, and so weak that at times she was unable to continue her work.

In February or March, 1899, she had an acute illness lasting from two to three weeks, and marked by fever, severe pain in the region of the spleen, distention of the abdomen with tenderness, particularly throughout the upper part. It is probable that at this time the infarct in the spleen and the adhesions to the omentum, subsequently to be mentioned, occurred.

In May she again applied to Dr. Harris. At this time she was quite weak and unable to work. The face appeared full and puffed, but the extremities were thin and the general weight reduced. The spleen extended from the seventh rib to a little below the crest of the ilium and about two to three centimetres to the right of the mid-line below the umbilicus. The characteristic notch in the border was easily felt. A brownish pigmentation was noted throughout the skin. This was marked about the face, neck, forearms, and particularly so over the abdomen about the umbilicus and extending down to the pubes. The skin of the abdomen had a distinctly mottled appearance. No pigmentation was noted about the gums or interior of the cheeks. No enlargement of any of the lymph-glands could be felt. The bowels were regular and the appetite, as a rule, good. The urine was amber in color, sp. gr. 1016; acid; no albumen; no sugar; microscopic examination negative. Blood examination showed:

Hæmoglobin (Fleischl)	40 per cent.
Red blood-cells	2,631,000
Leucocytes	2650
Color index	0.70

No plasmodium.

A differential count of the leucocytes was not made at this time. The pulse varied from 90 to 100; temperature, 98.6° F., and respiration, 24.

The case was now recognized as one of so-called splenic anæmia or primary splenomegaly, and splenectomy was advised as a curative measure. The patient readily consented to the operation, and the spleen was removed through a median incision, May 25, 1899. This spleen is minutely described later. The patient made an uninterrupted recovery. The blood count following the operation is of interest. At the end of the first twenty-four hours there were:

Reds	4,037,000
Whites	23,600

This increase in the number of red cells is probably only apparent, and due in part at least to the withdrawal of fluids as, during the first twenty-four hours, she was unable to take anything by the stomach, and the salt solution injected into the bowel was not retained. While this may partly explain the 50 per cent. increase in the red cells, it cannot explain the enormous increase in the leucocytes, amounting as it did to nearly 800 per cent. At the end of the second twenty-four hours, during which the patient took much fluid, there were:

Reds	2,800,000
Whites	15,000

Third twenty-four hours:

Reds	2,780,000
Whites	11,560

From now on the reds slightly increased, while the whites steadily decreased in number, so at the end of seventeen days there were:

Reds	3,250,000
Whites	5688

The urine was examined daily. For the first three days there seemed to be an absolute increase in the amount of the urea eliminated. The urea amounted to 22.3 grammes, while normally, according to her weight, there should have been but 18.4 grammes. By the sixth day the urea had dropped to twelve grammes, and remained at about that amount thereafter. At the end of thirty hours the temperature had reached 103.8° F. and the respiration 41, although the pulse remained at 100, just where it was before the operation. She continued to have a temperature varying from 99° to 101°, occasionally 102°, for about two weeks, when it gradually subsided. No local conditions could be found to account for the temperature, and the patient felt well.

Jonnesco (*Archiv für klinische Chirurgie*, Band lv, S. 330) says he has noticed elevation of temperature immediately after his splenectomies

which he attributed sometimes to pulmonary congestion. At other times no lesions were apparent, and he then thought it due to a reawakening of malaria in the system. My patient had never had malaria, and the cause of the temperature therefore must remain unknown. The patient left the hospital June 19 in good condition.

The subsequent history of this case is as follows: After leaving the hospital she continued to improve, and gained about twenty-five pounds in weight. September 1, she resumed her work. October 1, she began feeling badly about the stomach, especially after eating. After a few days she had considerable pain in the region of the stomach and vomited quite a little blood. She was obliged to take to her bed. The pains and vomiting continued for several days, but after the first day there was no longer any blood in the vomit. There was considerable gas formation in the intestines and colicky pains. After a temporary improvement she had a relapse, and returned to the hospital under the care of Dr. Harris, November 30. She was having considerable pain in the abdomen with marked tenderness over the region of the pancreas. Everything taken into the stomach was vomited. Temperature ranged from 101° to 102.4° F. Rectal nourishment was instituted and the stomach placed at rest. Improvement began at once. December 3, the blood count showed:

Reds	2,432,800
Whites	12,343

Stomach nourishment was resumed in a few days, and as the bowel movements were very offensive guaiacol carbonate was given. Improvement was progressive, and she left the hospital in good condition, December 17. December 23, a blood examination showed:

Hæmoglobin (Fleischl)	45 per cent.
Reds	3,173,440
Whites	9060
Color index	0.64

Differential count of the leucocytes showed:

Polynuclear neutrophiles	49.4 per cent.
Small mononuclears	23.4 per cent.
Large mononuclears	12.8 per cent.
Eosinophiles	14.4 per cent.
	100.0 per cent.

Attention is called to the very large percentage of eosinophiles.

Since this attack the patient has improved greatly in health and has had no further illness. During the past year she has been able to attend to her work and she has felt perfectly well, in fact, much better than she has for many years.

She has menstruated but twice since the operation, once in May, 1899, two days after the operation, and again in October, 1899, when she had the illness above mentioned. Since then there has been no sign of a menstrual flow.

When last examined, January 13, 1901, twenty months after the operation, it was noticed that the brown pigmentation of the skin, which was so marked before the operation, was rapidly disappearing. The face had a clearer and brighter color, and but a slight mottling, scarcely perceptible, remained over the abdomen. No enlarged lymph-glands were anywhere palpable. An examination of the urine showed nothing abnormal. The result of the blood examination was as follows:

Hæmoglobin	60 to 65 per cent.
Red blood-cells	3,776,000
White blood-cells	5200
Proportion of whites to reds	1 to 726
Color index	0.71 to 0.78

Differential count of the leucocytes:

Polynuclear neutrophiles	268 = 53.6	per cent.
Large mononuclear	106 = 21.2	per cent.
Small mononuclear	53 = 10.6	per cent.
Eosinophiles	57 = 11.4	per cent.
Transitional eosinophiles	4 = 0.8	per cent.
Basophiles	5 = 1.0	per cent.
Undefinable transitionals	7 = 1.4	per cent.
	500 100.0	per cent.

In regard to the blood examination, Dr. Herzog, who made the count, states: "When the differential count was made on cover-glass preparations treated with triacid and with glycerin-eosin-methylene-blue stains some peculiarities were observed which deserve notice. It was frequently difficult to distinguish between the small and the large mononuclears, and the former in general seemed larger than usual. The four corpuscles appearing in the above list as 'transitional eosinophiles' were polynuclears with few and very small eosinophilic granules. The basophiles (1 per cent.) were of the type of large mononuclears or of cells of a transitional character, and they contained a moderate number of coarse granules which stained with methylene blue. As transitional were classified such cells which could neither be grouped under large mononuclears nor under polynuclear neutrophiles. It was noticed that the blood contained more indistinct, hazy shadows of degenerating leucocytes than are usually seen." A large number of microcytes were also noticed.

The points of interest in this case are:

Its long duration.

The marked brownish pigmentation which gradually disappeared after removal of the spleen.

The high temperature lasting for two weeks after the operation without known cause.

The remarkable increase in the number of blood-cells, both red and white, immediately following the operation.

The increase in the reds was succeeded by a fall, and this in time by a gradual increase in number, which was of a more permanent character.

The great reduction in the number of reds which accompanied the peculiar sick spell about six months after the operation.

The return of the reds to a fairly good number which has remained now for more than a year.

The return of the leucocytes to the normal number, but with marked changes in the relative percentage of the different varieties.

The suspension of menstruation.

CASE II.—Mr. R., widower, American, forty-seven years of age. Travelling man by occupation. The family history is good. Both father and mother lived past eighty and died of heart disease. Five sisters are all living and well.

He had typhoid fever when three or four years of age and facial erysipelas twice, at the age of six and thirty respectively. Thinks he may have had some malaria at about the age of thirty, but was never very sick with it. There is no history of syphilis or gonorrhœa, nor has he been a drinking man. About two years ago he had an attack of la grippe. With the exceptions noted, he has always been healthy and strong.

He dates his present trouble from January, 1900, when he began having pains in the abdomen in the umbilical and epigastric regions. The pains were not particularly severe, nor could any exciting cause be assigned. Later his appetite gradually failed him and he was troubled with nausea. He had but one vomiting spell shortly before he entered the hospital, but there was nothing having the appearance of blood in the vomit. Associated with his condition were a progressive loss of strength and flesh. His loss in weight amounted to from thirty to forty pounds.

When he entered the Policlinic Hospital, September 16, 1900, he was very weak and considerably emaciated. His skin was of a dull, dirty, yellowish color, almost cachectic in appearance, but there was none of the brown pigmentation noted in Case I. His appetite was not good, and he

was troubled with nausea. The bowels moved nearly every day, but often not satisfactorily. There were no urinary symptoms.

An examination revealed nothing abnormal about the lungs or heart. The liver was not enlarged. In the left side of the abdomen was a large mass extending downward from beneath the left costal arch almost to the umbilicus and nearly to the mid-line, which, from its shape, location, mobility, etc., was considered to be an enlarged spleen. There was no enlargement of any of the palpable lymph-glands throughout the body. The temperature was normal; the pulse averaged 92, and the respiration 26 per minute. Urinalysis showed:

Amount passed in twenty-fours hours, 750 cubic centimetres;
Color, quite dark;
Reaction, acid;
Specific gravity, 1030;
Urea, 2 per cent.;
Albumen, none;
Sugar, none;
Bile, none;
Microscope, few oxalate of lime and urate crystals.

Blood examination:

Hæmoglobin (Fleischl)	Fifty per cent.
Red blood-cells	3,364,000
White blood-cells	28,200
Color index	0.74

The leucocytosis consisted in an increase in the polynuclear leucocytes. There were no myelocytes, no nucleated red blood-cells. No plasmodia were found. To sum up, we had here a case showing:

A markedly enlarged spleen without leukæmia.

There was no malaria or other pathologic condition to which the enlargement of the spleen could be attributed.

There was a moderate degree of anæmia with a diminished color index.

There was a progressive loss of strength and flesh.

Based upon these facts, a diagnosis of splenic anæmia or primary splenomegaly seemed justifiable, and removal of the enlarged organ was advised. Splenectomy therefore was performed September 28, 1900. The organ which was removed will be described in detail later.

The patient progressed slowly to recovery without incident of interest until October 21, when he had severe pain in the abdomen with distention and vomiting, and the bowels refused to move. Obstruction from adhesions was feared, and reopening of the abdomen considered. Next day, however, the bowels moved all right, and all unfavorable symptoms quickly disappeared. He had no further trouble.

For ten days after the operation his temperature ranged from 99° to 100° F., once reaching 101° on the second day. There were no local

conditions to which this temperature could be attributed, unless a slight bronchial irritation due to the ether was sufficient. There was no material change in the blood count during his stay in the hospital, although the tendency was to improvement. Thus a blood examination, October 19, 1900, showed:

Hæmoglobin (gravity test)	62½ per cent.
Red cells	3,864,000
White cells	24,000
Index	0.80

Differential count:

Small mononuclears	11.7 per cent.
Large mononuclears	9.2 per cent.
Polynuclear neutrophiles	78.0 per cent.
Eosinophiles	.8 per cent.
Transitional forms	.3 per cent.
Total	100.0 per cent.

Number counted 1000.

He left the hospital, October 25, 1900, in good condition. He lives out of the city, but has since been heard from as doing well and attending to his business.

That these cases are not identical is likely, for it seems probable there must be some differences between a case running a rapid course of a few months with a marked leucocytosis and a case protracted over several years with a marked leucopænia. Still, the cases are sufficiently characteristic to warrant their classification under that group to which the provisional term splenic anæmia or primary splenomegaly may be applied. The characteristic features of this group of cases are:

A considerable enlargement of the spleen;

An anæmia usually of moderate degree accompanied by a lowered color index;

An absence of the blood changes peculiar to leukæmia;

Loss of strength and weight; and, finally, it may be added that the condition is usually a progressive one with a tendency to a fatal termination. As a summary of the literature of the subject has been reviewed so recently by Sippy (*American*

Journal of the Medical Sciences, 1899, Vol. cxviii, pages 445-570), and the differential diagnosis so thoroughly considered by Osler (*American Journal of the Medical Sciences,* 1900, Vol. cxix, page 54), no attempt will be made to again go over this ground.

One statement, however, made by Sippy needs to be modified in view of more extensive experience. He states that the disease may terminate fatally in from five to six months, and that three and one-half years is the longest duration recorded. While the first part of this statement is probably correct, the last part must now be modified, as the disease in my first case had existed for at least nine years, and Osler reports several cases in which the condition had existed from five to twelve years.

Concerning the pathogenesis of this group of cases but little or nothing is known. It cannot even be stated with certainty in which organ or tissue the first changes make their appearance, although the evidence thus far obtained seems to point with great probability to the spleen as the part primarily at fault. The changes which take place in this organ will be described in detail later.

The changes which take place in the blood, so far as known, consist in a diminution in the number of erythrocytes with a reduction in the percentage of hæmoglobin, thus giving a lowered color index. So far as the leucocytes are concerned, there may be a leucocytosis (28,200, Case II) or a leucopænia (2600, Case I), usually the number is below normal. The differential count shows no characteristic changes.

After the removal of the spleen, however, a marked change is noted in the relative proportion of the different leucocytes, although the total number remains about normal. This change consists in a large increase in the percentage of eosinophiles. An eosinophilia has been observed in animals after removal of the spleen as well as in man (" Histology of the Blood," Ehrlich and Lazarus, 1900).

It requires some months for the eosinophilia to become marked. In Case I, seven months after the operation, the

eosinophiles formed 14.4 per cent. of the total number of the leucocytes, and twenty months after the operation, 11.4 per cent. Another change noted is an increase in the percentage of the large mononuclears. In Case I, these, at the end of seven months, had increased to 12.8 per cent., and at the end of twenty months to 21.2 per cent. The significance or explanation of these changes in the relative proportion of the leucocytes cannot at present be given.

While it is freely admitted that the cases so far recorded and the facts at present at our disposal are not sufficient to warrant any positive deductions concerning the histogenesis of splenic anæmia, it may not be amiss to consider some points in this connection.

One of the important questions to decide is: Does the anæmia precede and cause the enlargement of the spleen, or is it secondary thereto? Jawein (*Virchow's Archiv für Path. Anat.,* 1900, Vol. xvi, p. 461) has shown that a pathologic destruction of red blood-cells is always followed by an enlargement of the spleen. This was found to be true clinically as well as experimentally. By the introduction of erythrolytic substances (chlorate of potash) into the blood of animals he was able to produce an enlargement of the spleen at will, and, furthermore, there seemed to be a direct relation between the degree of enlargement and the number of red cells destroyed. He therefore concludes that the chief function of the spleen is to remove dead red blood-cells from the circulation, and that such dead cells have the specific property of stimulating this function. Thus is explained the enlargement of the spleen which takes place in certain infectious diseases, chronic malarial poisoning, etc., conditions in which an abnormal destruction of erythrocytes occurs.

At first sight, it would not seem unreasonable to apply the facts brought to light by Jawein's experiments to splenic anæmia; to suppose that, owing to some unknown cause, there was a persistent abnormal destruction of the blood-cells, which dead cells, through their specific effect on the spleen, excite an enlargement of this organ.

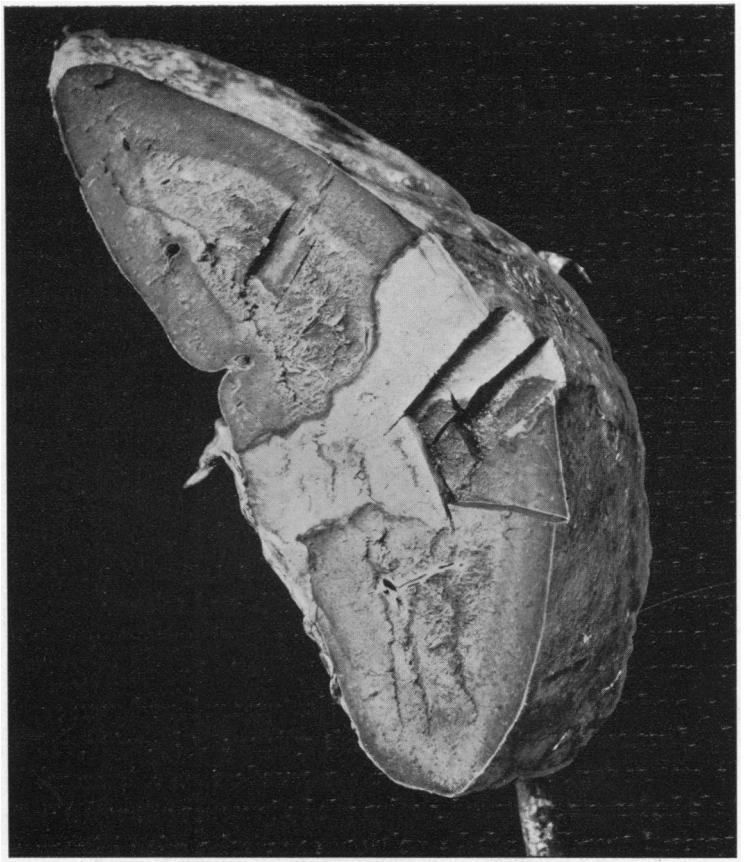

FIG. 1.—Section of spleen removed in Case I, showing infarct.

While this explanation appears quite simple and specious, there are facts which speak strongly against it. The most forcible of these is the fact that apparently perfect recovery follows removal of the spleen. The erythrocytes immediately begin to increase in number and the general condition of the blood improves.

It is impossible to reconcile this with the supposition that the splenic enlargement is secondary to the anæmia, that it is,

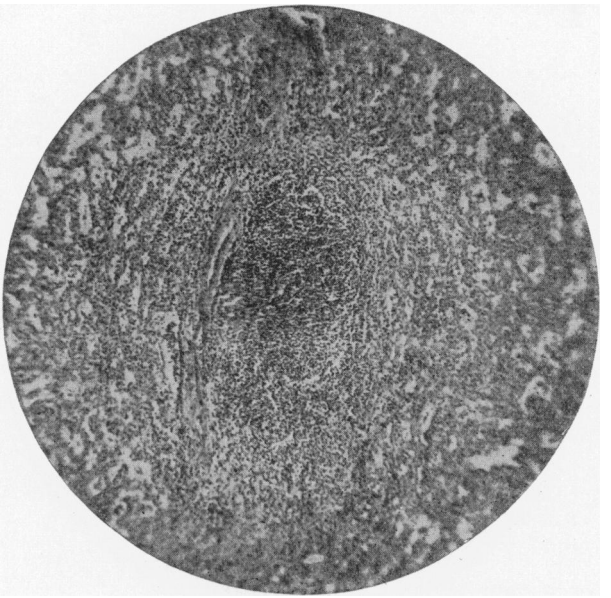

FIG. 2.—Malpighian body surrounded by enlarged blood lymph spaces of splenic pulp. Photomicrograph from Case II.

in a sense, a hypertrophy due to increased activity. It seems, therefore, much more probable that the splenic enlargement is primary, be its cause what it may, and that the anæmia is dependent thereon. This does not elucidate, however, the essential nature of the disease. Let us now consider the changes found in the spleen.

Macroscopic Description.—The spleen removed in our first case had retained its shape fairly well; it is enlarged in all of its dimensions. Its diameters are 21 by 13.5 by 7 centi-

metres. Weight, after having been hardened in 4 per cent. watery formalin solution, 1055 grammes. The surface is smooth on the whole, except in a few places where it had formed adhesions to the omentum. The organ is harder in consistency than normal. A wedge-shaped infarct extends from the hilum to the upper surface. Capsule thickened.

The spleen in our Case II is of the typical spleen shape and uniformly enlarged in all of its dimensions. Diameters: 18 by 12½ by 6 centimetres. Weight, after having been

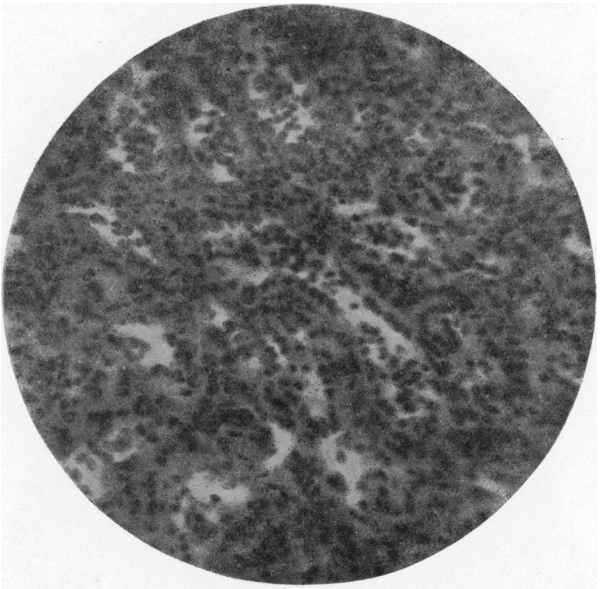

FIG. 3.—Enlarged blood lymph spaces of splenic pulp. Photomicrograph from Case II.

hardened in a 4 per cent. watery formalin solution, 600 grammes. Surface slightly uneven and wrinkled; capsule highly thickened; spleen tissue somewhat firmer than normal, however not as firm as in Case I. The surface shows a few grayish white spots.

Histopathology.—In studying the histopathology of splenomegaly, one is confronted with the difficulty that there are still a number of disputed points in the histology of the

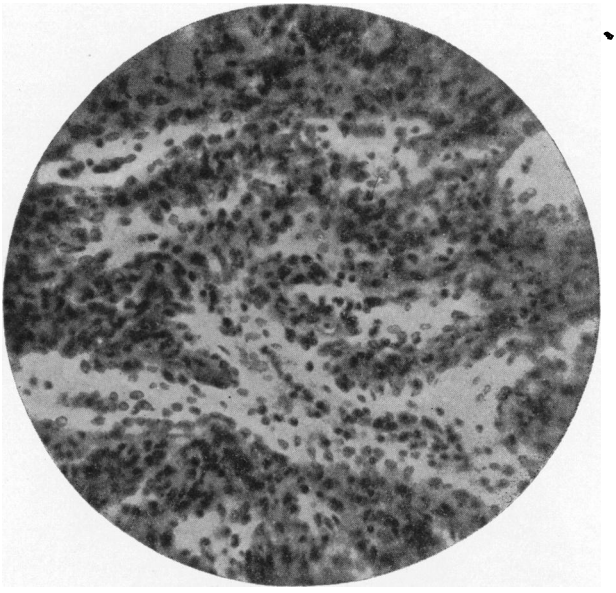

FIG. 4.—Enlarged blood lymph spaces of splenic pulp. Photomicrograph from Case II.

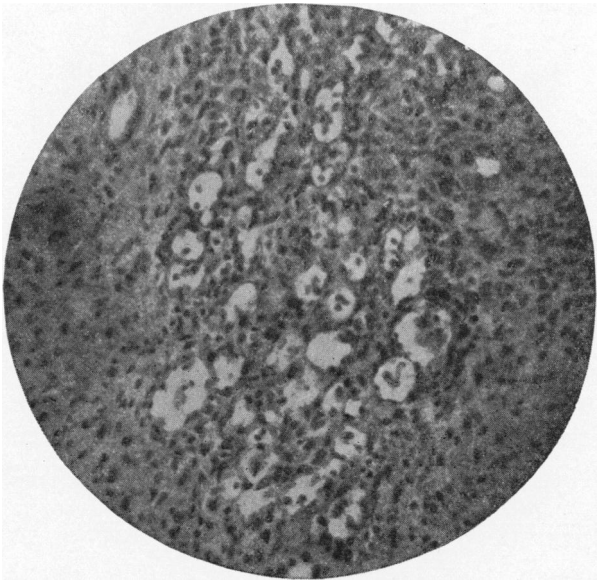

FIG. 5.—Enlarged blood lymph spaces of splenic pulp. Photomicrograph from Case I.

normal spleen, and that normal human splenic material is almost beyond one's reach.

Among the latest contributions to the normal histology of the spleen are those of Bannwarth and Kultschitzky. The papers of Hoyer have not been accessible to us, and the latest contribution of Mall has very little bearing upon our histopathologic considerations.

Bannwarth,[1] from his investigations, comes to the conclusion that there exists in the splenic pulp an open intermediary blood space with a common blood and lymph circulation. The common blood lymph spaces in the splenic pulp are, however, generally not lined by endothelial cells.

Kultschitzky[2] gives the following summary of his

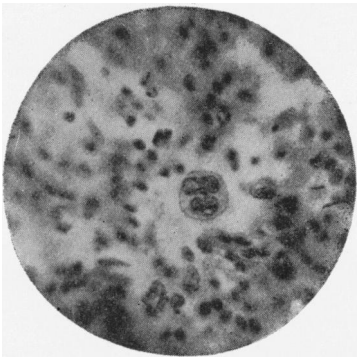

FIG. 6.—Giant cell with four nuclei. Photomicrograph from Case I.

views: "I now feel compelled (in opposition to views held formerly) to admit that there exists in the spleen an open blood circulation, as was first described by W. Müller. I am now adopting this view partly in consequence of the more recent contributions of Hoyer, G. Hoyer, Bannwarth, and Sokolow, and partly in consequence of my own personal observations. . . . We, therefore, find that older observations as well as those of the most recent date concerning the normal

[1] Untersuchungen über die Milz Archiv für Mikroscop. Anat., 1891, Vol. xxxviii, p. 345, and Neuere Milzuntersuchungen, etc. Correspondenzbl. für Schweizer Aerzte, 1893, Vol. xxiii, p. 586.

[2] Zur Frage über den Bau der Milz Archiv für Mikroscop. Anat., 1895, Vol. xlvi, p. 673.

histology of the spleen establish the fact that there exists in its pulp open blood-spaces. These latter are formed by connective-tissue fibres and cells, and they partly show an incomplete lining with endothelial-like cells. Split arterial capillaries and small arteries pour their blood into the lymph-clefts of the pulp. The blood here mixes with the lymph and the mixture is carried away by venous capillaries and veins."

If, now, after this consideration of the normal histology of the spleen, we turn to the histopathology of splenomegaly primitive, we find only few extensive and correct contributions to the subject.

It may be stated here that the histologic changes in splenomegaly consist chiefly in a proliferation of endothelial elements as they have been described very recently in a most excellent manner by Bovaird,[1] who, however, is not the first author to observe the endothelial hyperplasia in splenic anæmia.

Gaucher described the endothelial proliferation in 1882 in a "Thèse de Paris," but he had then wrongly interpreted what he saw, and spoke of an "Hypertrophie idiopathique de la rate sans leucémie," or an "épithélioma primitif de la rate." In 1892, however, he gives a somewhat modified description, and clearly states that the proliferated cells which he mentions are of connective tissue and not of epithelial origin. He describes these cells as "cellules nuclées d'aspect épithélial," and he says that they owe their origin to a "proliferation irritative des éléments conjonctifs sous l'influence d'une cause encore inconnue."

Picou, in 1895, reported a splenectomy for splenomegaly, and he also describes the large proliferated epithelial-like cells, and mentions that some contain two to three nuclei. He states these cells are endothelial cells, and he calls the condition of the spleen an "endothélioma primitif." Cornil, speaking about Picou's case, thinks that the condition is one of primary hypertrophy of the spleen with proliferation of the elements of the pulp.

[1] Primary Splenomegaly Endothelial Hyperplasia of the Spleen, The American Journal of the Medical Sciences, October, 1900.

Collier[1] reports a case of a child six years old in whom the spleen began to enlarge at the age of two. At the post-mortem the spleen weighed four pounds two ounces. The author states that on microscopic examination the splenic reticulum is seen to be replaced by very large endothelial cells. It is stated that an older sister of the child likewise suffered from a fatal enlargement of the spleen.

Williamson[2] reports a case of splenomegaly with microscopic examination of the spleen. The patient was a boy nine years old, who was admitted to the Manchester Royal Infirmary on February 15, 1892. A blood examination showed red blood-corpuscles, 3,030,000; white blood-corpuscles, 4000; hæmoglobin, 22 per cent. July 14, 1892, the child died.

The histological examination was much complicated by the fact that the child died of typhoid fever. Strange to say, the author denies that death was due to typhoid, but the macroscopic and microscopic findings clearly show it. Post-mortem examination demonstrated ulceration in ileum, perforation at the site of one ulcer, general peritonitis, endocarditis of the mitral valve. Microscopically the spleen showed fibrous trabeculæ much thickened, fibroid changes of Malpighian bodies, splenic pulp congested, and the sinuses contained large and small nucleated cells. The most striking feature was the presence of enormous numbers of large nucleated cells, each containing a number of red blood-corpuscles. These large phagocytic cells which are characteristic of typhoid changes were observed by Billroth as early as 1862, and they have been described fully recently by Mallory.[3]

Sippy in his case describes the histology of the spleen as follows: "The majority of the Malpighian corpuscles show only slight alterations. Many appear normal, others present a slight increase in the reticular tissue, and now and then a Malpighian body is found which shows considerable sclerosis.

[1] A case of enlarged spleen in a child six years old. Transactions of the London Pathological Society, 1895, Vol. xlvi, p. 148.

[2] Cases of anæmia with great enlargement of the spleen, Manchester Medical Chronicle, 1893, Vol. xviii, p. 103.

[3] A Histologic Study of Typhoid Fever, Journal of the Boston Society of Medical Sciences, April, 1898, also Journal of Experimental Medicine.

No marked degenerative changes are to be seen in the cells. The veins show a moderate increase in the connective tissue which surrounds them, areas are found where this increase is very marked. Fibrous tissue extends some distance into the splenic pulp, enclosing within its meshes lymphoidal cells, isolated and in groups. In many places the pulp appears normal; however, in general, it is apparent that the reticulum is considerably increased. Here and there are to be found areas of marked sclerosis containing lymphoidal cells in the meshes of the fibrous issue."

We now come to the most recent publication upon the subject, namely, that of Bovaird, who reports two cases:

CASE I was that of a girl who, at the age of three years, was first seen in November, 1896. Swelling of the spleen was diagnosed, and the blood examination gave the following result: Red corpuscles, 4,400,000; leucocytes, 9000; hæmoglobin, 75 per cent. The child was again seen after three years (1899). The abdomen at the umbilicus now had a circumference of twenty-three and one-fourth inches. Examination of the blood was as follows:

Red corpuscles	4,180,000
Leucocytes	14,000
Hæmoglobin	62 per cent.
Polynuclear	57.5 per cent.
Large lymphocytes	29 per cent.
Small lymphocytes	12.5 per cent.
Eosinophiles	1 per cent.

CASE II was an older sister of Case I. When first seen in November, 1896, she was thirteen years old. Enormous swelling of spleen was present, which first began to show itself when the child was three years old.

Blood examination:

Red corpuscles	2,880,000
Leucocytes	4000
Hæmoglobin	60 per cent.

In 1899, or when sixteen years old, the splenic tumor was larger, and a blood examination showed:

Red corpuscles	3,550,000
Leucocytes	7000
Hæmoglobin	not given
Large lymphocytes	15 per cent.
Small lymphocytes	21 per cent.
Polynuclears	62 per cent.
Eosinophiles	1.4 per cent.

Splenectomy, May 17, 1899; death three hours after the operation. Spleen after removal weighed twelve and one-half pounds. Shape in general that of a normal spleen.

Bovaird in his very extensive microscopic description states that the pulp spaces are much enlarged, lined by large endothelial cells, and often contain masses of proliferated endothelia. There are also found polynuclear giant cells. On other places there is found a fibrous connective tissue, and pictures are seen which suggest the transformation of the large endothelial cells into fibrous connective tissue. The abdominal lymph-nodes and the lymph-clefts of the liver likewise show masses of proliferated endothelial cells.

The author raises the question: Is this a diffuse endothelioma of the spleen with metastasis in the abdominal lymph-nodes and the liver? This he answers in the negative. He considers the changes in the spleen those of a diffuse endothelial hyperplasia, and believes that the same morbid influences which caused the splenic changes also produced an endothelial hyperplasia in the abdominal lymph-nodes and in the liver.

Histopathology of Our own Cases.—(The material which had been hardened in dilute watery formalin was embedded in paraffin, and the sections were studied with a variety of stains.) Case II shows the changes which have taken place much clearer than Case I, so its microscopy will be described first and more fully.

CASE II.—The capsule of the spleen is thickened and consists of a fibrous connective tissue, rather poor in nuclei. Weigert's elective stain shows a number of elastic fibres. The trabeculæ are likewise thickened and contain the same tissue elements as the capsule. The latter as well as the former contain a few involuntary muscle fibres. The Malpighian corpuscles in general show few changes. Here and there evidences of a sclerosis are manifest. This is particularly seen in the cortical portion of some Malpighian bodies where the fibrous connective tissue is markedly increased and the lymphoid elements proportionately decreased. The most marked changes are found in the splenic pulp. The simple clefts of the pulp, partly and incompletely lined with endothelia, have disappeared, and all lumina seen possess a complete endothelial lining. The condition is such that it is impossible to say with certainty what has originally belonged to the capillaries and what to the pulp lymph-clefts.

The endothelia which line the common blood lymph spaces have not the character of normal flat vascular endothelia, but are cubical cells with comparatively large vesicular nuclei fairly rich in chromatin. The medium-sized cell protoplasm is finely granular and stains well with eosin. Quite a number of karyokinetic figures are seen in the endothelial cells. In

some places the proliferation of these cells has been so lively that numbers of dropped-off endothelia are seen in the lumina. Some of the cells contain two, three, and four nuclei. The open blood lymph spaces also contain a large number of leucocytes, viz., lymphocytes, neutrophile polynuclear leucocytes, and eosinophiles. Red blood-corpuscles are not found in any numbers in the pulp spaces. This must be due to the fact that the blood was allowed to escape from the spleen after its removal. It is very probable that, as the blood ran out, almost all of the erythrocytes escaped, while the more sticky leucocytes were held back.

In spite of the fact that the open spaces are not completely filled, they are mostly found gaping and open. This is due to the fact that they have thick walls. This expression, however, is not quite correct. The wall proper of the spaces is really only formed by a single layer of endothelia, but the lumina are separated from each other by rather thick tissue septa. These show very little fibrous connective tissue, but are almost wholly made up of connective-tissue cells of an embryonal character, which, in appearance, are very similar to the endothelia described. Bovaird states that he saw in his case pictures which strongly suggest the transformation of the endothelia into connective-tissue fibres. Anything like this cannot be well seen in our case. But such a change is by no means improbable. The splenic pulp shows an abundant infiltration with hæmosiderin and hæmatoidin. Large phagocytic cells containing included erythrocytes were not seen, but some of the endothelial cells contain hæmatoidin and hæmosiderin granules.

CASE I shows histologic changes similar to Case II. They are, however, not so clearly demonstrable. The pulp spaces are collapsed in many places, and the endothelial lining is not so uniformly present. The ischæmic infarct shows the usual changes, namely, necrobiosis of the cellular elements with loss of staining properties of the nuclei. The tissues contained in the zone of the infarct still show to a large extent the original structure. The amount of fibrin found in the infarcted area is not large. The infarct thus appears of recent origin. Surrounding the infarct is a hyperæmic zone with blood extravasation and migration of leucocytic elements into the ischæmic area.

From the above description it appears obvious that the chief histologic changes found in splenomegaly consist in an endothelial proliferation, an endothelial hyperplasia. The French first looked upon the changes found in splenomegaly as an epithelioma, but later called it an " endothélioma primitif de la rate." Cornil has opposed this view, and so has Bovaird. We also wish to express our belief that the changes found in splenomegaly cannot be looked upon as a diffuse endothelioma. We are of the opinion that the process is one resembling somewhat that found in lymphangioma. In the latter condition, as

in splenomegaly, there is present a proliferation of lymphatic endothelia with enlargement and new formation of lymph spaces. The changes characteristic of lymphangioma have been described by Virchow, Klebs, Vegner, Tilger, Nasse, and others, and also by one of the authors in a short paper published some time ago.

It appears to us, from its histopathology, that splenomegaly may be looked upon as a process similar to a diffuse lymphangioma. Ischæmic infarcts either in the shape of one large infarct or as a number of small infarctions have been described a number of times in splenomegaly. These infarcts probably owe their origin to cell thrombi formed by the numerous leucocytic elements found in the enlarged lymph-blood spaces.

The next question which must engage our attention is: Can the pathologic changes in the spleen explain the progressive deterioration of the blood which is found in splenomegaly? It may be considered as established that red corpuscles are normally destroyed in the spleen. It appears at first sight not at all unlikely that red corpuscles are disintegrated in the spleen through the agency of phagocytic endothelial cells.

One is tempted to assume that an increase in the endothelial elements in the splenic pulp would be followed by an increase in the number of blood-corpuscles destroyed. Yet, tempting as this hypothesis is in explanation of the progressive blood deterioration in splenomegaly, it lacks tangible evidence. We have in vain searched our sections for phagocytic cells containing red blood-corpuscles; nor does the literature on splenomegaly contain any statement to this effect. The one case cited in which such phagocytic cells were found was complicated with typhoid fever, and therefore proves nothing.

Another explanation of the *modus operandi* of the destruction of red blood-corpuscles in splenomegaly may be offered. The dissolution of senile blood-corpuscles, or those damaged by toxic influences, may not be brought about directly by the phagocytic action of certain splenic cells, but by an erythrolytic enzyme formed in and secreted by certain splenic cells. If we assume that the endothelial cells of the splenic

pulp furnish this erythrolytic enzyme, an easy explanation is offered for the great blood destruction in splenomegaly. These endothelia are enormously increased in splenomegaly, and if they do secrete an erythrolytic enzyme the latter would be increased very much. If we remove the spleen, we remove the source of the increased amount of the erythrolytic enzyme, and the blood destruction comes to a stand-still. It is also obvious that there must be other organs—the lymph-nodes—which have a moderate erythrolytic function, which comes into play more prominently after splenectomy. It appears, however, that the lymph-nodes cannot completely substitute the erythrolytic function of the spleen. It was noticed in our Case I that twenty months after splenectomy the blood contained quite a number of indistinct, hazy blood-corpuscles, and many microcytes.

One thing appears certain, namely, that the changes in the spleen must in some way be responsible for the blood deterioration in splenomegaly, otherwise removal of the changed spleen would not be such an excellent therapeutic measure as it appears to be.

Treatment.—The treatment of splenic anæmia from a medical stand-point has not proved successful. Attention is therefore particularly directed to the value of splenectomy in this class of cases.

Sippy gives an incomplete list of cases of primitive splenomegaly in which a splenectomy was performed. He cites the following cases:

CASE I.—Operator, Spencer Wells; date, 1865; female, aged thirty-four years; weight of spleen, *2672* grammes. Result: death.

CASE II.—Operator, Péan; date, 1876; female, aged twenty-four years; weight of spleen, 1125 grammes. Result: In one month patient had recovered perfectly; subsequently died of toxic enteritis.

CASE III.—Operator, Czerny; date, 1878; female, aged thirty years; weight of spleen not given; size, *23* by 12 by 8 centimetres. Result: Complete cure.

CASE IV.—Operator, Franzolini; date, 1881; female, aged twenty-two years; weight of spleen, 1526 grammes. Result: Complete cure.

CASE V.—Operator, Frascani; female, aged sixteen years; weight of spleen, 1310 grammes. Result: Death from hæmorrhage in four hours.

CASE VI.—Operator, Ceci; date, 1893; female, aged thirteen years; weight of spleen, 1300 grammes. Result: Recovery.

CASE VII.—Operator, Lindfors; date, 1892; female, aged twenty years; size of spleen, 25 by 15 by 7 centimetres. Result: Recovery.

To this list the following cases have to be added:

Banti (Splenomegalie mit Lebercirrh. Ziegler's *Beiträge,* 1898, Vol. xxiv, p. 21) reports three cases of splenomegaly with cirrhosis of the liver, operated upon by F. Colzi.

CASE VIII.—Operator, Colzi; woman. Result: Died several days after the operation from a septic puerperal complication.

CASE IX.—Operator, Colzi; young man. Result: In best of health thirty-three months after the operation.

CASE X.—Operator, Colzi; woman. Result: Was in good health twenty-one months after the operation. No anæmia.

CASE XI.—Operator, Power (Successful removal of an enlarged and displaced spleen. *British Medical Journal,* 1900, November 17, p. 1428); widow, forty-three years old; operated September 6, 1899. Three and a half years ago she struck her left side just over the lower ribs. Two years later she noticed the lower part of her abdomen increasing in size. At the operation the spleen was found suspended from a pedicle four inches long, consisting of fatty connective tissue with large veins and splenic artery. After removal the estimated weight of the spleen was two and one-half pounds. It weighed seventeen to eighteen ounces after having been in alcohol for six months. The blood examination eight days after the operation showed:

Red corpuscles	4,230,000
White corpuscles	17,000
Lymphocytes	18.75 per cent.
Large mononuclear	12.5 per cent.
Polynuclear	65.5 per cent.
Eosinophiles	3.5 per cent.

No myelocytes.

The patient recovered.

CASE XII.—Operator, Cushing (Splenectomy for primary splenic anæmia. *Maryland Medical Journal,* Baltimore, 1899, Vol. xli, p. 140). The short report states that a splenectomy was made for splenic anæmia. Patient made a good recovery and gained thirty pounds in weight.

CASE XIII.—Osler. Man, aged thirty-three years. Trouble of ten years' duration:

Red blood-corpuscles	3,000,000
Leucocytes	2800
Hæmoglobin	25 per cent.

Differential count:

Polymorphonuclears	84.4 per cent.
Small mononuclears	4.4 per cent.
Large mononuclears	5 per cent.
Transitionals	3.4 per cent.
Eosinophiles	2.8 per cent.

Splenectomy; patient recovered; continued well one year after operation.

CASE XIV is one of Bovaird's cases, which has been referred to more fully above. Girl, sixteen years old. Patient died three hours after the operation.

CASE XV.—Picou (Epithélioma primitif de la rate de Gaucher. *Bull. de la Soc. Anat. de Paris,* 5e Ser., 1895, Vol. ix, p. 531) reports a successful splenectomy in a woman thirty-two years old. The spleen weighed 2800 grammes and was 26½ by 14.2 by 9 centimetres.

CASE XVI.—Gaucher (De l'hypertrophie idiopathique de la rate sans leucémie *La France Médicale,* 1892, Vol. xxxix, p. 529) mentions that among three specimens of splenomegaly which he examined, there was one in which the spleen had been removed by an operation. No further details are given about this splenectomy.

CASE XVII.—M. Tscherniachowski (Hildebrand's *Jahresbericht für Chic.,* 1899, S. 720), a twenty-five-year-old woman. Duration of tumor five years. Diagnosed as essential hypertrophy of spleen. Splenectomy was performed on account of constant increase in the size of the spleen, with loss of strength in spite of treatment. Complete recovery.

To this list of splenectomies for primitive splenomegaly we can add the two cases above recorded. This then makes a list of nineteen cases, with fourteen recoveries, four deaths, and one case where the result is not stated. A mortality of a little over 20 per cent. This is certainly a very favorable showing for splenectomy.

There may be some question as to the propriety of including Banti's three cases in this list, but, as two of them recovered and were reported well thirty-three and twenty-one months respectively after the operation, it would seem that the splenomegaly was the primary and chief condition and the cirrhosis of the liver secondary thereto, and that they are therefore justly entitled to be included.

Concerning the after history of the cases that recovered, unfortunately, but little is said. In eight cases it is simply stated the patients recovered and were well, but the length of time after the operation at which the observations were made was not stated. In one case the time is specified as one year after the operation; in one case twenty-one months, and in another thirty-three months. It is to help fill in this gap that the subsequent history of our Case I was entered into in such detail, as it has now been under observation about twenty-two months.

If it can be shown, as now seems probable, that these cases do recover after splenectomy, not simply recover from the operation but regain fully their health and well being, it will establish splenectomy as the proper line of treatment in these cases, as, up to this time, medicinal treatment is acknowledged to be unsuccessful. As the difficulties as well as the dangers of the operation increase in proportion to the size of the spleen, it is advisable to operate as soon as a correct diagnosis can be established and the futility of medicinal treatment is made evident.

Concerning the technique of the operation there is but little to add. The median incision is the one most desirable in the majority of cases. Most of the operators who have removed enlarged spleens recommend dividing the gastrosplenic omentum between ligatures first, and freeing the upper end of the organ from the vault of the diaphragm in order to turn it out of the abdomen before ligating the pedicle proper. The difficulties in reaching the gastrosplenic omentum with an enlarged spleen in place are often very great, as most writers have stated; therefore, after attempting to follow this method in our first case, it was abandoned.

The incision was extended downward so that the lower end of the spleen could be drawn upward. The splenic vessels were then easily approached and ligated. The veins in these cases are enormously dilated, and so thin that they are easily punctured or lacerated in attempting to pass the ligature needle.

It is probably better to ligate at once than to place a large clamp on the vessels with the intention of ligating after the organ is removed, as the thin veins are apt to tear at the edge of the clamp during the subsequent manipulations, and great difficulty may be experienced in again getting control of the hæmorrhage. This was experienced in the second case.

After ligating and dividing the pedicle, the spleen may be drawn downward and the gastrosplenic omentum more easily gotten at.